Methodology of Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES-cardiac): A randomized clinical trial in cardiac surgery patients

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Background: Postoperative delirium (POD) is a geriatric syndrome characterized by acute onset, fluctuating severity, confusion, disorganized thinking, and inattention. [1] It can affect up to 70% of patients over the age of 60 following a major surgical procedure. [2] Risk factors include age, male sex, mild cognitive impairment, dementia, and psychiatric conditions. [2,3] POD risk factors have also been identified which are specific to cardiac surgery (i.e., type of surgery, transfusions, cardiopulmonary bypass, oxygen desaturations). [4] POD is associated with an increased risk of falls, increased health care costs, prolonged hospitalizations, reductions in independence, and increased mortality. [5-10]

Studies have suggested that using the bispectral index (BIS) for guidance in titrating the level of general anesthesia can reduce the incidence of POD. [2,11-13] Fritz et al (2016) [14] reported that EEG burst suppression is an independent risk factor for the onset of POD. Several studies also demonstrated a relationship between low intraoperative BIS (associated with EEG burst suppression) and postoperative mortality. [5,15-20]

Similar to EEG burst suppression, cerebral desaturation has been associated with POD following cardiac surgery. [21] Intraoperative cerebral desaturations are very common during bypass surgery and occur in 50-70% of patients. [22,23] However, a recent systematic review [24] revealed that only low level evidence links cerebral oximetry to cognitive outcomes following cardiac surgery.

Studies outlined above suggest that anesthesia may be a modifiable risk factor for the development of POD but there are no validated anesthetic protocols aimed at modifying its onset and/or severity. Even the routine use of BIS and EEG remains controversial, in part based on several clinical trials that question whether EEG-guidance meaningfully changes anesthetic administration in real world settings. [25-27]

Our primary objective is to determine whether the depth of anesthesia (and specifically EEG burst suppression) is a modifiable risk factor for the onset of POD. Secondary objectives are to determine whether an EEG-guided anesthesia protocol can modify the severity of POD, and reduce the incidence of other associated negative events (falls, mortality, psychiatric illness). And finally, determine how EEG burst suppression and cerebral oximetry relate to one another.
We hypothesize that elderly patients who undergo cardiac surgery with the EEG-guided anesthesia protocol will have a reduced incidence of POD (and downstream negative events) compared to the patients who undergo cardiac surgery with anesthesia guided by routine methods.

Methods: ENGAGES-Cardiac is a multi-centre, double-blinded, randomized control trial. Kingston General Hospital (KGH) is one of 6 participating Canadian centers. Patients >60 years of age scheduled to undergo elective on-pump cardiac surgery and are competent to provide informed consent are included in the study. Exclusion criteria includes all patients undergoing non-cardiac or off-pump cardiac surgery, patients with a history of delirium or intraoperative awareness under general anesthesia, and patients that are blind, deaf, illiterate or not fluent in English.

Patients will be randomized to receive standard-of-care anesthesia or standard of care anesthesia plus collection of EEG information which will be used to aid in anesthetic titration. The allocation will be concealed until entry into the OR and initiation of anesthesia at which point the randomization assignment will be revealed to the anesthesiologist and the surgeon with instructions not to disclose. The patients and assessors will remain blinded until study completion. Likewise, anesthetists carrying out the study protocol will remain blinded to all outcomes.

All patients will have 2 adhesive strips attached to their head; one for BIS-guidance and the other for near infrared spectroscopy (NIRS) to measure intraoperative oxygen levels. Anesthesiologists in the intervention arm will have access to raw and processed EEG waveforms, including BIS, during surgery and will use the occurrence of burst suppression as the primary trigger to reduce the dose of anesthetic. The same information will be collected in the standard-of-care group, but the anesthesiologist will be blinded to this information and will continue to guide anesthesia as per their usual standard approach.

Sample size: A total of 1232 patients will be recruited across all Canadian sites, with the sample size based on a previously published meta-analysis of studies using BIS-guided anesthesia.[23] Using a conservative estimate of 25% incidence of postoperative delirium following standard anesthesia, with a two-sided P<0.05, a total of 1232 patients will be required to detect a hazard ratio of 0.70 at 80% power. We will recruit 200 from our site at KGH. Together, we expect recruitment from all sites to be completed within the first year to allow final follow-up data collection by the end of the second year.

Interim analyses: Patient recruitment is currently ongoing. An interim analysis will be conducted after randomization of 200 subjects across all centers. The analysis will compare the time in burst suppression between the EEG-guided group and the routine care group using a Student t-test. A second interim analysis will be undertaken after 600 randomized subjects have been discharged.